

**PROTOCOL TITLE : Randomized, double blind, placebo controlled, multicenter pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF)**

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**LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS**

<b>ACE</b>	<b>Angiotensin-converting enzyme</b>
<b>AHF</b>	<b>Acute Heart Failure</b>
<b>ABR</b>	<b>ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)</b>
<b>AE</b>	<b>Adverse Event</b>
<b>AESI</b>	<b>Adverse Events of Special Interest</b>
<b>ARB</b>	<b>Angiotensin Receptor Blocker</b>
<b>AUC</b>	<b>Area Under the Curve</b>
<b>BNP</b>	<b>B-type Natriuretic Peptide</b>
<b>C<sub>max</sub></b>	<b>Maximum observed concentration</b>
<b>BI</b>	<b>Boehringer Ingelheim bv Netherlands</b>
<b>BI KG</b>	<b>Boehringer Ingelheim GmbH &amp; Co KG Germany</b>
<b>CA</b>	<b>Competent Authority</b>
<b>CCMO</b>	<b>Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek</b>
<b>CV</b>	<b>Curriculum Vitae</b>
<b>DKA</b>	<b>Diabetic Ketoacidosis</b>
<b>DSMB</b>	<b>Data Safety Monitoring Board</b>
<b>eGFR</b>	<b>Estimated glomerular filtration rate</b>
<b>ECG</b>	<b>Electrocardiogram</b>
<b>EU</b>	<b>European Union</b>
<b>EudraCT</b>	<b>European drug regulatory affairs Clinical Trials</b>
<b>GCP</b>	<b>Good Clinical Practice</b>
<b>HF</b>	<b>Heart Failure</b>
<b>IB</b>	<b>Investigator's Brochure</b>
<b>IC</b>	<b>Informed Consent</b>
<b>JVP</b>	<b>Jugular Venous Pressure</b>
<b>IMP</b>	<b>Investigational Medicinal Product</b>
<b>IMPd</b>	<b>Investigational Medicinal Product Dossier</b>
<b>METC</b>	<b>Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)</b>
<b>MRA</b>	<b>Mineralocorticoid receptor antagonist</b>
<b>NT-</b>	<b>n-terminal-prohormone brain natriuretic peptide</b>

<b>proBNP</b>	
<b>P-gp</b>	<b>P-Glycoprotein</b>
<b>(S)AE</b>	<b>(Serious) Adverse Event</b>
<b>SGLT-2</b>	<b>Sodium dependent Glucose Transporter –2</b>
<b>SPC</b>	<b>Summary of Product Characteristics (in Dutch: officiële productinformatie IB1-tekst)</b>
<b>Sponsor</b>	<b>The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.</b>
<b>SUSAR</b>	<b>Suspected Unexpected Serious Adverse Reaction</b>
<b>UGT</b>	<b>UDP- Glycosyltransferase</b>
<b>ULN</b>	<b>Upper Limit of Normal</b>
<b>VAS</b>	<b>Visual Analogue Scale</b>
<b>Wbp</b>	<b>Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgegevens)</b>
<b>WMO</b>	<b>Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)</b>



## SUMMARY

**Rationale:** Acute decompensated heart failure is the fastest growing disease in the world and the leading cause of hospital admissions worldwide. Short term mortality and rehospitalization are extremely high (20-30% within 3-6 months) and there is no therapy available that improves clinical outcome in these patients. Empagliflozin is a selective inhibitor of sodium glucose co-transporter with diuretic and renal-protective properties. In patients with type 2 diabetes at high risk for cardiovascular events, empagliflozin reduced the risk of hospitalization for heart failure by 35%. Based on the promising pharmacological profile of empagliflozin in relation to the needs for treatment of acute decompensated heart failure, we hypothesize that empagliflozin exerts positive effects in acute decompensated heart failure, with or without diabetes.

### **Objectives:**

#### Primary Objective:

The primary objective of this trial is to evaluate whether empagliflozin 10 mg/ day will relieve dyspnea, improves diuretic response, decreases length of initial hospital stay and plasma NT-proBNP levels compared to placebo in patients who are admitted for acute decompensated heart failure.

#### Secondary Objectives:

The secondary objectives of this trial are to evaluate the effects of empagliflozin on death and/or heart failure re-admission to Day 30 and on plasma and urinary markers of renal function and injury.

#### Safety Objectives:

The safety objectives of this trial are to evaluate whether empagliflozin is well tolerated, and does not cause an excess number of (serious) adverse events. Specific attention will be paid to hypotension, renal dysfunction, ketoacidosis and/ or hyperosmolar hyperglycemic syndrome.

**Study design:** This is a randomized, placebo-controlled, double-blind, parallel group, multicenter study in subjects admitted for acute decompensated heart failure. Eighty eligible subjects will be randomized in a 1:1 ratio to receive either empagliflozin 10 mg/day or matched placebo.

**Study population:**Inclusion Criteria:

1. Male or female >18 years of age; Women of non-child-bearing potential must have a documentation of surgical sterilization (hysterectomy and/or bilateral oophorectomy) OR must have experienced menopause (no menses for >12 months). Women of child bearing potential must have a negative pregnancy test, AND must use highly effective methods of contraception during treatment with the investigational product plus 5 days after the end of study drug administration.
2. Hospitalized for AHF; AHF is defined as including all of the followings measured at any time between presentation (including the emergency department) and the end of screening:
  - a. Dyspnea at rest or with minimal exertion
  - b. Signs of congestion, such as edema, rales, and/or congestion on chest radiograph
  - c. BNP  $\geq 350$  pg/mL or NT-proBNP  $\geq 1,400$  pg/mL (for patients with atrial fibrillation: BNP  $\geq 500$  pg/mL or NT-proBNP  $\geq 2,000$  pg/mL)
  - d. Treated with loop diuretics at screening
3. Able to be randomized within 24 hours from presentation to the hospital
4. Able and willing to provide freely given written informed consent
5. eGFR (CKD-EPI)  $\geq 30$  mL/min/1.73m<sup>2</sup> between presentation and randomization

Exclusion Criteria:

1. Diabetes Mellitus type 1
2. Dyspnea primarily due to non-cardiac causes
3. Cardiogenic shock
4. Acute coronary syndrome within 30 days prior to randomization
5. Planned or recent percutaneous or surgical coronary intervention within 30 days prior to randomization
6. Signs of keto-acidosis and/or hyperosmolar hyperglycemic syndrome (pH < 7.30 and glucose > 15 mmol/L and HCO<sub>3</sub><sup>-</sup> < 18 mmol/L)
7. Pregnant or nursing (lactating) women
8. Current participation in any interventional study
9. Inability to follow instructions or comply with follow-up procedures
10. Any other medical conditions that may put the patient at risk or influence study results in the investigator's opinion, or that the investigator deems unsuitable for the study

**Intervention:** In this study patients are randomized in a 1:1 ratio to receive an oral once daily dose of 10 mg empagliflozin or matching placebo tablet, both on top of standard of care.

**Main study parameters/ endpoints:**

Primary endpoints:

To estimate the mean response and associated variability for a) Dyspnea relief, assessed by VAS at baseline to Day 4 (or discharge if earlier); b) Diuretic response (defined as  $\Delta$  weight kg/[(total i.v. dose)/40mg]+[(total oral dose)/80mg]) furosemide (or equivalent loop diuretic dose) up to Day 4); c) Length of initial hospital stay; d) Change in NT-proBNP from baseline to Day 4 (or discharge if earlier)

Secondary endpoints:

- Death and/or heart failure re-admission to Day 30
- Change in plasma values of renal function, including creatinine, eGFR, cystatin C, BUN, neutrophil gelatinase associated lipocalin (NGAL), kidney injury molecule (KIM-1), fibroblast growth factor 23 (FGF-23) and hemoglobin, hematocrit, albumin from baseline to Day 4 (or discharge if earlier)
- Change in other plasma values of renal function, including creatinine, cystatin C, BUN, neutrophil gelatinase associated lipocalin (NGAL), kidney injury molecule (KIM-1), fibroblast growth factor 23 (FGF-23) and hemoglobin, hematocrit, albumin from baseline to Day 30
- Change in urinary sodium excretion and urinary levels of markers of glomerular and tubular function, including urinary albumin excretion (UAE), N-acetyl-beta-D-glucosaminase (NAG), NGAL and KIM-1, from baseline to Day 4 (or discharge if earlier)
- Change in urinary sodium excretion and urinary levels of markers of glomerular and tubular function, including urinary albumin excretion (UAE), N-acetyl-beta-D-glucosaminase (NAG), NGAL and KIM-1, from baseline to Day 30

Safety endpoints:

- Adverse events and serious adverse events
- One specific adverse event of special interest (AESI) will be a deterioration of eGFR to an absolute value below 20 mL/min/1.73m<sup>2</sup> within the first 5 days of hospitalization.
- Vital signs
- ECGs
- Laboratory evaluations

- Worsening heart failure to Day 5 post randomization (or discharge if earlier), defined as worsening signs and/or symptoms of heart failure that require an intensification of intravenous therapy for heart failure or mechanical ventilatory, renal or circulatory support.

**Nature and extent of the burden and risks associated with participation, benefit and group relatedness:**

- Patients will visit the hospital more often than they would usually do (2 times per year instead of 1 time per year)
- Patients will take extra medication, on top of their usual medication
- Rare cases of diabetic ketoacidosis (DKA), some of which were life threatening, have been reported in patients treated with SGLT2 inhibitors, among which was empagliflozin. In some cases, only moderately elevated glucose levels, below 14 mmol/l, were reported. In case of non-specific symptoms like nausea, vomiting, anorexia, abdominal pain, excessive thirst, respiration difficulties, confusion, unusual fatigue or somnolence, diabetic ketoacidosis should be ruled out. In case of diabetic ketoacidosis, use of empagliflozin should be stopped immediately.
- In patients hospitalized for surgery or acute severe medical conditions, empagliflozin treatment should be interrupted until the patient is stabilized again.
- Although cases of liver damage were reported, causal relationship between empagliflozin and liver damage has not been shown.
- Haematocrit elevations have been reported.
- Elderly patients (older than 75 years) are at risk of dehydration as a result of empagliflozin treatment. Fluid intake should be monitored, notably in case of concomitant treatment with ACE inhibitors and diuretics.
- Blood pressure may drop significantly.
- In case of circumstances which may lead to fluid loss, careful monitoring of fluid status and electrolytes is warranted.

**Procedures:**

- Patient-reported AHF symptoms will be collected using a Visual Analog Scale (VAS) describing symptom severity at each point in time. These evaluations will be done daily from start of study drug administration up to Day 4 or discharge, if earlier.
- Patients will have clinical evaluations, including AHF symptom assessments, fluid balance and recording of type and dose of diuretic drugs, fluid and sodium restrictive regimens, vital signs, physical examination emphasizing signs of HF, as well as an assessment of need for

further IV HF treatment and worsening HF events (for definition: see endpoints) at least daily to the earlier of Day 5 or discharge.

- Blood will be collected for clinical chemistry and hematology assessments, and urine specimens will be collected daily during the first days of treatment for routine safety assessments and to evaluate renal function to the earlier of Day 5 or discharge and at the Day 30 visit.
- The occurrence of adverse events and serious adverse events, mortality and hospital readmission for HF will be assessed at the Day 30 visit and Day 60 phone call.
- Safety will be assessed by recording medical history, monitoring adverse events and vital signs, and performing physical examinations and routine clinical laboratory tests as per the protocol, as well as those felt to be clinically indicated by the investigator. Adverse events (AE) and serious adverse events (SAE) will be collected up to Day 60 from start of study drug administration.
- One specific AESI will be the deterioration of eGFR within the first 5 days of hospitalization (and randomized treatment) to an absolute value below ( $<$ ) 20 mL/min/1.73m<sup>2</sup>.
- Measurements of pH, Lactate, HCO<sub>3</sub> and glucose will be performed daily up to Day 5 or discharge, if earlier to monitor for signs and symptoms of ketoacidosis and/or hyperosmolar hyperglycemic syndrome. In case keto-acidosis is suspected, further assessments will be done and diagnostic criteria as defined by the American Diabetes Association will be followed and safety stopping rules will be applied.
- During the initial phase of hospitalization, patients will be continuously monitored for possible rhythm and/or conduction disorders at least during the first 24 hours of treatment.

## 1. INTRODUCTION AND RATIONALE

Acute decompensated heart failure is one of the fastest growing diseases in the world and a leading cause of hospital admissions worldwide.(1) Short term mortality and rehospitalization are extremely high (20-30% within 3-6 months). There is no therapy available that improves clinical outcome of these patients.(2) Therefore, there is a very high unmet need to find effective treatments in patients with acute decompensated heart failure. Despite treatment with loop diuretics, many patients are discharged with residual congestion, which is related to a higher risk of early rehospitalization and death. Renal Failure and worsening renal function in patients with AHF is common and related to an impaired outcome. Empagliflozin is a selective inhibitor of sodium glucose co-transporter with diuretic and renal protective properties. Recently, empagliflozin reduced the risk of cardiovascular outcome and of death from any cause in patients with type 2 diabetes at high risk for cardiovascular events.(3) Interestingly, hospitalization for heart failure was reduced by 35% and risk of progression of nephropathy by 44%.(4) We hypothesize that the reduction in the risk of hospitalization for heart failure was caused by the diuretic and renal protective properties of empagliflozin and that empagliflozin is therefore beneficial for the treatment of patients who are hospitalized for acute decompensated heart failure.

## 2. OBJECTIVES

### Primary Objective:

The primary objective of this trial is to evaluate whether empagliflozin 10mg/day will relieve dyspnea, improves diuretic response, decreases length of initial hospital stay and plasma NT-proBNP levels compared to placebo in patients who are admitted for acute decompensated heart failure.

### Secondary Objective:

The secondary objectives of this trial are to evaluate the effects of empagliflozin on death and/or heart failure re-admission to Day 30 and on plasma and urinary markers of renal function and injury.

### Safety Objectives:

The safety objectives of this trial are to evaluate whether empagliflozin is well tolerated, and does not cause an excess number of (serious) adverse events. Specific attention will be paid to hypotension, renal dysfunction, ketoacidosis and/ or hyperosmolar hyperglycemic syndrome.

### 3. STUDY DESIGN

This is a randomized, placebo-controlled, double-blind, parallel group, multicenter study in subjects admitted for acute decompensated heart failure. Eighty eligible subjects will be randomized in a 1:1 ratio to receive either empagliflozin 10 mg/day or matched placebo.

Duration and setting: Patients hospitalized for acute decompensated heart failure will be randomly assigned to empagliflozin or placebo (on top of standard of care treatment including loop diuretics) within 24 hours after admission. The intended duration of treatment will be 30 days after randomization.

### 4. STUDY POPULATION

#### 4.1 Population (base)

Patients with an acute hospital admission for decompensated heart failure. These patients will usually present at the emergency department and/or at the cardiac care unit.

#### 4.2 Inclusion Criteria

1. Male or female >18 years of age; Women of non-child-bearing potential must have a documentation of surgical sterilization (hysterectomy and/or bilateral oophorectomy) OR must have experienced menopause (no menses for >12 months). Women of child bearing potential must have a negative pregnancy test, AND must use highly effective methods of contraception during treatment with the investigational product plus 5 days after the end of study drug administration.
2. Hospitalized for AHF; AHF is defined as including all of the followings measured at any time between presentation (including the emergency department) and the end of screening:
  - a. Dyspnea at rest or with minimal exertion
  - b. Signs of congestion, such as edema, rales, and/or congestion on chest radiograph
  - c. BNP  $\geq 350$  pg/mL or NT-proBNP  $\geq 1,400$  pg/mL (for patients with AF: BNP  $\geq 500$  pg/mL or NT-proBNP  $\geq 2,000$  pg/mL)
  - d. Treated with loop diuretics at screening
3. Able to be randomized within 24 hours from presentation to the hospital
4. Able and willing to provide freely given written informed consent
5. eGFR (CKD-EPI)  $\geq 30$  ml/min/1.73m<sup>2</sup> between presentation and randomization

### 4.3 Exclusion Criteria

1. Diabetes Mellitus type 1
2. Dyspnea primarily due to non-cardiac causes
3. Cardiogenic shock
4. Acute coronary syndrome within 30 days prior to randomization
5. Planned or recent percutaneous or surgical coronary intervention within 30 days prior to randomization
6. Signs of ketoacidosis and/or hyperosmolar hyperglycemic syndrome ( $\text{pH} > 7.30$  and glucose  $> 15$  mmol/L and  $\text{HCO}_3^- > 18$  mmol/L)
7. Pregnant or nursing (lactating) women
8. Current participation in any interventional study
9. Inability to follow instructions or comply with follow-up procedures
10. Any other medical conditions that may put the patient at risk or influence study results in the investigator's opinion, or that the investigator deems unsuitable for the study

### 4.4 Sample size calculation

Sample size:  $n=80$  (40 patients per study arm)

With 40 patients in the control group, a given mean continuous response can be estimated within  $\pm 0.2$  Standard deviations (SD) with 80% confidence. We estimate the following mean responses for continuous outcome:

1. Change in dyspnea VAS score:  $1756 \pm 2353$  mmxh,
2. Diuretic response (of  $0.56 \pm 0.78$  kg/40 mg Furosemide (or equivalent))
3. Length of stay 9.6 to 10.5 days ( $\pm 9.1$ )
4. Percentage change in NT-proBNP 24 ( $-1.0 - 88.7$ )% (SD 67% assuming normal distribution) (all at 96 hours (day 4))

Binary outcomes, such as event rates of Death and/or HF re-admission at 60 days have occurred in approximately 10-15% of patients in AHF studies (RELAX-AHF and PROTECT studies). A rate of 10% can be estimated within  $\pm 6.1\%$  and a rate of 15% within  $\pm 7.2\%$  with 80% confidence.

#### Treatment effect:

As this is an exploratory analysis the overall power to establish small treatment effects is limited. Forty patients per group provides approximately 80% power to detect standardized mean treatment differences of approximately 0.48 SDs at the two-sided 20% significance level, which gives around the following differences: dyspnea VAS score of 1129 mmxh,



Diuretic response of 0.37 kg/40 mg Furosemide, Length of initial hospital stay of 4 days, and percentage change in NT-proBNP of 32%, with the above mentioned estimates of mean response in the control group.

As an additional, exploratory analysis, and for graphical presentation, individual responses will be standardized (i.e., the difference from the overall mean divided by the overall SD) and aligned so that a bigger value represents a better outcome; log-rank scores for time-to-event outcomes will be thus standardized; and treatment effects presented as mean differences in standardized scores with 80% CIs. As a measure of overall response to treatment, the average standardized score across the 4 outcomes will be computed for each patient, and the mean treatment difference and associated 95% CI for this average standardized score presented.

## **5. TREATMENT OF SUBJECTS**

### **5.1 Investigational product/treatment**

Patients will be treated once daily with 10 mg empagliflozin tablets or matching placebo tablets. The tablets can be taken with or without food, swallowed whole with water. If a dose is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day.

### **5.2 Use of co-intervention (if applicable)**

Simultaneous use of oral antidiabetics and heart failure treatment (diuretics, ACE inhibitors, ARBs, Betablockers, and MRA as per standard local practice) is allowed.

Special attention should be paid to possible interactions for simultaneous use.

Empagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension. Insulin and insulin secretagogues, such as sulphonylureas, may increase the risk of hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with empagliflozin.

Co-medication with known inducers of UGT enzymes should be avoided due to a potential risk of decreased efficacy. An interaction study with gemfibrozil, an in vitro inhibitor of OAT3 and OATP1B1/1B3 transporters, showed that empagliflozin C<sub>max</sub> increased by 15% and AUC increased by 59% following coadministration. These changes were not considered to be clinically meaningful. Inhibition of OATP1B1/1B3 transporters by co-administration with rifampicin resulted in a 75% increase in C<sub>max</sub> and a 35% increase in AUC of empagliflozin. These changes were not considered to be clinically meaningful.

Empagliflozin exposure was similar with and without co-administration with verapamil, a P-gp inhibitor, indicating that inhibition of P-gp does not have any clinically relevant effect on empagliflozin. Interaction studies conducted in healthy volunteers suggest that the pharmacokinetics of empagliflozin were not influenced by co-administration with metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, simvastatin, torasemide and hydrochlorothiazide. Drug-drug interactions involving the major CYP450 and UGT isoforms with empagliflozin and concomitantly administered substrates of these enzymes are considered unlikely. Empagliflozin does not inhibit P-gp at therapeutic doses. Based on in vitro studies, empagliflozin is considered unlikely to cause interactions with drugs that are P-gp substrates. Interaction studies conducted in healthy volunteers suggest that empagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, simvastatin, warfarin, ramipril, digoxin, diuretics and oral contraceptives.

### **5.3 Escape medication (if applicable)**

Not applicable

## **6. INVESTIGATIONAL PRODUCT**

### **6.1 Name and description of investigational product(s)**

#### Active study medication:

Film coated tablets, containing 10 mg empagliflozin and lactose monohydrate, equivalent to 154,3 mg water free lactose. Other ingredients are: micro crystalline cellulose, hydroxypropylcellulose, croscarmellose sodium, colloid water free siliciumdioxide, magnesium stearate, hypromellose, titanium dioxide (E171), talk, macrogol 400, and ferric oxide yellow (E172).

Placebo matching 10 mg empagliflozin tablets contain the same ingredients, except empagliflozin.

Study medication will be provided by Boehringer Ingelheim Pharma GmbH & Co. KG (BI KG).

### **6.2 Summary of findings from non-clinical studies**

Please refer to the SPC of empagliflozin.

### **6.3 Summary of findings from clinical studies**

Please refer to IMPD of empagliflozin.

#### 6.4 Summary of known and potential risks and benefits

- Rare cases of diabetic ketoacidosis (DKA), some of which were life threatening, have been reported in patients treated with SGLT2 inhibitors, among which was empagliflozin. In some cases, only moderately elevated glucose levels, below 14 mmol/l, were reported. In case of non-specific symptoms like nausea, vomiting, anorexia, abdominal pain, excessive thirst, respiration difficulties, confusion, unusual fatigue or somnolence, diabetic ketoacidosis should be ruled out. In case of diabetic ketoacidosis, use of empagliflozin should be stopped immediately.
- In patients hospitalized for surgery or acute severe medical conditions, empagliflozin treatment should be interrupted until the patient is stabilized again.
- Diabetes Type I patients should not be treated with empagliflozin
- Although cases of liver damage were reported, causal relationship between empagliflozin and liver damage has not been shown.
- Haematocrit elevations have been reported.
- Elderly patients (older than 75 years) are at risk of dehydration as a result of empagliflozin treatment. Fluid intake should be monitored, notably in case of concomitant treatment with ACE inhibitors and diuretics.
- Blood pressure may drop significantly.
- In case of circumstances which may lead to fluid loss, careful monitoring of fluid status and electrolytes is warranted.

#### 6.5 Description and justification of route of administration and dosage

The 10 mg oral tablets are the registered formulation of empagliflozin (Jardiance<sup>®</sup>).

#### 6.6 Dosages, dosage modifications and method of administration

Patients will receive one 10 mg tablet empagliflozin/placebo once daily during 30 days.

##### 6.6.1. Stopping rules and discontinuation criteria

The administration of study drug will need to be discontinued if a patient experiences any of the following events during study drug administration:

- A drop in systolic blood pressure below 90 mmHg OR a symptomatic systolic blood pressure decrease between 90 and 100 mmHg accompanied by signs and/or symptoms related to hypotension.
- Signs of ketoacidosis and/or hyperosmolar hyperglycemic syndrome (pH < 7.30 and glucose > 15 mmol/L and HCO<sub>3</sub> < 18 mmol/L). In case of non-specific symptoms like

nausea, vomiting, anorexia, abdominal pain, excessive thirst, respiration difficulties, confusion, unusual fatigue or somnolence, diabetic ketoacidosis should be ruled out.

- Any increase of serum creatinine >50%.

## **6.7 Preparation and labelling of Investigational Medicinal Product**

Study medication will be prepared and labelled by BI KG and delivered to the participating sites.

## **6.8 Drug accountability**

Study medication will be ordered by TCC and shipped in tranches to the participating sites. Batches will be decided upon based on inclusion rate, in order to avoid an excess number of study medication reaching the expiry date. Shipments will be documented by Boehringer Ingelheim. Study medication is stored under the requested storage conditions in the hospital pharmacy. Study drug kits are assigned to the patient by using the IVRS system, made available by TCC.

Study medication will be released by the respective hospital pharmacies on an individual patient basis and every release is documented. Dispensing and collection of returned study medication will be executed and documented by the investigators and used medication is stored in the hospital pharmacies.

Upon closure of the study, used and unused study medication is documented by the sites and returned to the local hospital pharmacy, who will document receipt and who will destroy the study medication. Destruction will be documented as well.

## **7. NON-INVESTIGATIONAL PRODUCT**

Not Applicable.

## **8. METHODS**

### **8.1 Study parameters/endpoints**

#### **8.1.1 Main study parameter/endpoint**

##### Primary endpoints:

To estimate the mean response and associated variability for a) Dyspnea relief, assessed by VAS at baseline to Day 4 (or discharge if earlier); b) Diuretic response (defined as  $\Delta$  weight kg/[(total i.v. dose)/40mg]+[(total oral dose)/80mg]) furosemide (or equivalent loop diuretic dose) up to day ;c) Length of initial hospital stay; d) Change in NT-proBNP from baseline to Day 4 (or discharge if earlier)

### 8.1.2 Secondary study parameters/endpoints (if applicable)

#### Secondary endpoints:

- Death and/or heart failure re-admission to Day 30
- Change in plasma values of renal function, including creatinine, eGFR, cystatin C, BUN, neutrophil gelatinase associated lipocalin (NGAL), kidney injury molecule (KIM-1), fibroblast growth factor 23 (FGF-23) and hemoglobin, hematocrit, albumin from baseline to Day 4 (or discharge if earlier)
- Change in other plasma values of renal function, including creatinine, cystatin C, BUN, neutrophil gelatinase associated lipocalin (NGAL), kidney injury molecule (KIM-1), fibroblast growth factor 23 (FGF-23) and hemoglobin, hematocrit, albumin from baseline to Day 30
- Change in urinary sodium excretion and urinary levels of markers of glomerular and tubular function, including urinary albumin excretion (UAE), N-acetyl-beta-D-glucosaminase (NAG), NGAL and KIM-1, from baseline to Day 4 (or discharge if earlier).
- Change in urinary sodium excretion and urinary levels of markers of glomerular and tubular function, including urinary albumin excretion (UAE), N-acetyl-beta-D-glucosaminase (NAG), NGAL and KIM-1, from baseline to day 30

### 8.1.3 Other study parameters (if applicable)

#### Safety endpoints:

- Adverse events and serious adverse events
- One specific AESI will be a deterioration of eGFR to an absolute value below 20 mL/min/1.73m<sup>2</sup> within the first 5 days of hospitalization.
- Vital signs
- ECGs
- Laboratory evaluations
- Worsening heart failure to Day 5 post randomization (or discharge if earlier), defined as worsening signs and/or symptoms of heart failure that require an intensification of intravenous therapy for heart failure or mechanical ventilatory, renal or circulatory support.

## 8.2 Randomisation, blinding and treatment allocation

Subjects will be randomised 1:1 to active or placebo treatment. Randomisation will be executed by using the IVRS system. Treatment assignment will take place by the Trial Coordination Center, University Medical Center Groningen, the Netherlands. Patients will maintain this randomisation number throughout the study. Randomisation will be executed in blocks of 4 patients in order to maintain balanced randomisation in each participating site.

## 8.3 Study procedures

### 8.3.1 Screening

At screening, the following assessments will be executed:

- Written informed consent
- Demographic data
- Medical history by chart review and interviewing of the patient
- Supine vital signs after 5 minutes rest (systolic and diastolic blood pressure, heart rate, respiratory rate)
- Physical examination, including weight, height (only at screening), edema, rales, JVP, orthopnea assessment
- 12-lead electrocardiogram (ECG)
- NYHA class assessment
- Screening BNP/NT-proBNP and pregnancy test (local lab)
- Clinical lab chemistry panel (Na, K, BUN, creatinine, haemoglobin, Ht, lactate, glucose,  $\text{HCO}_3^-$ , pH), haematology and urinalysis
- Concomitant medication
- Adverse eventsIn- and exclusion criteria

### 8.3.2 Baseline (0 hours)

After having confirmed eligibility by confirming all inclusion criteria and by ruling out either one of the exclusion criteria, the following assessments will be executed:

- Randomization
- Supine vital signs after 5 minutes rest (systolic and diastolic blood pressure, heart rate, respiratory rate)
- Physical examination, including weight, edema, rales, JVP, orthopnea assessment
- NYHA class assessment
- Clinical lab chemistry panel (Na, K, BUN, creatinine, haemoglobin, Ht, lactate, glucose,  $\text{HCO}_3^-$ , pH, NT-proBNP ), haematology and urinalysis at local lab
- Collection of two EDTA blood samples for biomarker analysis and buffy coat for genetic analysis
- Collection of one Urine sample for biomarker analysis
- Dyspnea VAS
- Fluid balance by measuring ingested and excreted fluid volumes
- Start of 24 hour continuous Holter ECG monitoring

- Study drug dispensing and administration
- Concomitant medication
- Adverse events

### 8.3.3 Day 1 (24 hours)

On Day 1, the following assessments will be executed:

- Supine vital signs after 5 minutes rest (systolic and diastolic blood pressure, heart rate, respiratory rate)
- Physical examination, including weight, edema, rales, JVP, orthopnea assessment
- NYHA class assessment
- Clinical lab chemistry panel (Na, K, BUN, creatinine, haemoglobin, Ht, lactate, glucose,  $\text{HCO}_3^-$ , pH, NT-proBNP), haematology and urinalysis at local lab
- Collection of two EDTA blood samples for biomarker analysis
- Collection of one Urine sample for biomarker analysis
- Dyspnea VAS
- Fluid balance by measuring ingested and excreted fluid volumes
- End of 24 hour continuous Holter ECG monitoring
- Study drug dispensing and administration
- Concomitant medication
- Adverse events
- AESI, including drop in eGFR below 20 mL/min/1.73m<sup>2</sup>

### 8.3.4 Day 2 (48 hours)

On Day 2, the following assessments will be executed:

- Supine vital signs after 5 minutes rest (systolic and diastolic blood pressure, heart rate, respiratory rate)
- Physical examination, including weight, edema, rales, JVP, orthopnea assessment
- NYHA class assessment
- Clinical lab chemistry panel (Na, K, BUN, creatinine, haemoglobin, Ht, lactate, glucose,  $\text{HCO}_3^-$ , pH, NT-proBNP), haematology and urinalysis at local lab
- Collection of two EDTA blood samples for biomarker analysis
- Collection of one Urine sample for biomarker analysis
- Dyspnea VAS

- Fluid balance by measuring ingested and excreted fluid volumes
- Study drug dispensing and administration
- Concomitant medication
- Adverse events
- AESI, including drop in eGFR below 20 mL/min/1.73m<sup>2</sup>

#### **8.3.5 Day 3 (72 hours)**

On Day 3, the following assessments will be executed:

- Supine vital signs after 5 minutes rest (systolic and diastolic blood pressure, heart rate, respiratory rate)
- Physical examination, including weight, edema, rales, JVP, orthopnea assessment
- NYHA class assessment
- Clinical lab chemistry panel (Na, K, BUN, creatinine, haemoglobin, Ht, lactate, glucose, HCO<sub>3</sub><sup>-</sup>, pH, NT-proBNP) , haematology and urinalysis at local lab
- Dyspnea VAS
- Fluid balance by measuring ingested and excreted fluid volumes
- Study drug dispensing and administration
- Concomitant medication
- Adverse events
- AESI including drop in eGFR below 20 mL/min/1.73m<sup>2</sup>
- 2 Blood samples (EDTA) for biomarker analysis
- Collection of one Urine sample for biomarker analysis

#### **8.3.6 Day 4 (96 hours)**

On Day 4, the following assessments will be executed:

- Supine vital signs after 5 minutes rest (systolic and diastolic blood pressure, heart rate, respiratory rate)
- Physical examination, including weight, edema, rales, JVP, orthopnea assessment
- including NYHA class assessment
- Clinical lab chemistry panel (Na, K, BUN, creatinine, haemoglobin, Ht, lactate, glucose, HCO<sub>3</sub><sup>-</sup>, pH, NT-proBNP), haematology and urinalysis at local lab
- Dyspnea VAS
- Fluid balance by measuring ingested and excreted fluid volumes
- Study drug dispensing and administration



- Concomitant medication
- Adverse events
- AESI including drop in eGFR below 20 mL/min/1.73m<sup>2</sup>
- 2 Blood samples (EDTA) for biomarker analysis
- Collection of one Urine sample for biomarker analysis

#### **8.3.7 Day 5 (120 hours)**

On Day 5, the following assessments will be executed:

- Supine vital signs after 5 minutes rest (systolic and diastolic blood pressure, heart rate, respiratory rate)
- Physical examination, including edema, rales, JVP, orthopnea assessment
- NYHA class assessment
- Clinical lab chemistry panel (Na, K, BUN, creatinine, haemoglobin, Ht, lactate, glucose, HCO<sub>3</sub><sup>-</sup>, pH, NT-proBNP), haematology and urinalysis at local lab
- Study drug dispensing and administration
- Concomitant medication
- Adverse events
- AESI, including drop in eGFR below 20 mL/min/1.73m<sup>2</sup>

#### **8.3.8 Day 30 (+ 3 days) On site visit**

On Day 30, the following assessments will be executed:

- Supine vital signs after 5 minutes rest (systolic and diastolic blood pressure, heart rate, respiratory rate)
- Physical examination, including edema, rales, JVP, orthopnea assessment
- NYHA class assessment
- Abbreviated clinical lab chemistry panel (Na, K, BUN, and creatinine, NT-proBNP), urinalysis measured at local lab
- EDTA Blood sample for biomarker analysis
- Collection of one Urine sample for biomarker analysis
- Study drug return/ tablet count
- Concomitant medication
- Adverse events

#### **8.3.9 Day 60 (+ 5 days) Phone call**

On Day 60, the following assessments will be executed:

- Telephone contact with patient in which the occurrence of Adverse events will be questioned

## Schedule of Events

Timepoint	Screen	Baseline	D1	D2	D3	D4	D5	D30 (+ 3d) visit	D60 (+ 5d) phone call
<b>Procedures/ Assessments</b>									
ICF	x								
Medical history	x								
Vital signs (BP, HR, RR)	x	x	x	x	x	x	x	x	
Physical exam incl. HF assessment <sup>a, b</sup>	x	x	x	x	x	x	x	x	
Weight	x	x	x	x	x	x		x	
ConMed	x	x	x	x	x	x	x	x	
Adverse Events	x	x	x	x	x	x	x	x	x
ECG	x								
Incl/Excl criteria	x								
Randomization		x							
Dyspnea VAS		x	x	x	x	x			
NYHA assessment	x	x	x	x	x	x	x	x	
Fluid balance		x	x	x	x	x			
Study drug administration		x	x	x	x	x	x	x <sup>d</sup>	
Holter ECG monitoring <sup>c</sup>		x	x						
<b>Local Lab</b>									
Screening BNP/NT-proBNP	x								
Serum pregnancy	x								
Chemistry, Hematology, Urinalysis <sup>e</sup>	x	x	x	x	x	x	x	x <sup>f</sup>	
<b>Central Lab</b>									
Biomarkers		x	x	x	x	x		x	

<sup>a)</sup> HF assessments: Edema, rales, JVP, orthopnea

<sup>b)</sup> Height to be measured at screening

<sup>c)</sup> To be performed during the first 24 hours of study drug administration

<sup>d)</sup> Final study drug administration if visit occurs on Day 30, study drug return and tablet count

<sup>e)</sup> Including the measurement of pH, Lactate, HCO<sub>3</sub> and glucose

<sup>f)</sup> Abbreviated Chemistry panel on Day 30 (Sodium, Potassium, BUN and creatinine), urinalysis

## **8.4 Withdrawal of individual subjects**

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

### **8.4.1 Specific criteria for withdrawal (if applicable)**

Not applicable

## **8.5 Replacement of individual subjects after withdrawal**

Withdrawn subjects will not be replaced.

## **8.6 Follow-up of subjects withdrawn from treatment**

Subjects withdrawn from treatment will be asked whether the investigator will be allowed to contact the patient regularly during the study in order to collect information regarding vital status and eventual (serious) adverse events. Investigators will be urged to have subjects consent to them gathering follow-up information of each withdrawn subject.

## **8.7 Premature termination of the study**

The study may be prematurely terminated if either one or more of the following criteria apply:

- Request by the independent Data Safety Monitoring Board to prematurely terminate the study because of safety or futility reasons
- Apparent inability to include sufficient subjects
- Bankruptcy of the sponsor

## **9. SAFETY REPORTING**

### **9.1 Temporary halt for reasons of subject safety**

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

## 9.2 AEs, SAEs and SUSARs

### 9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. Adverse events (AE) will be recorded from randomization to Day 30. Serious adverse events (SAE) and adverse events of special interest (AESI) are to be reported from randomization up to the Day 60 phone call.

### 9.2.2 Adverse Events of Special Interest (AESI)

According to Boehringer Ingelheim standard requirements, Adverse Events of Special Interest (AESI) will be collected throughout the study, simultaneously with the collection of Adverse Events.

The following AESI will be collected:

- Hepatic injury

A hepatic injury is defined by the following alterations of hepatic laboratory parameters after randomisation:

- An elevation of AST and/or ALT  $\geq 3$  fold ULN combined with an elevation of total bilirubin  $\geq 2$  fold ULN measured in the same blood sample
- An isolated elevation of ALT and/or AST  $\geq 5$  fold ULN

These laboratory findings constitute a hepatic injury alert and the patients showing these abnormalities need to be followed up according to medical abnormalities need to be followed up according to medical judgement.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without laboratory results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test

- Worsening Renal Function

either defined by:

drop in eGFR below ( $<$ ) 20 mL/min/1.73m<sup>2</sup> in the first 5 days of randomized treatment

or

A serum creatinine value showing  $\geq 2$  fold increase from baseline and is above the ULN.

For the AESI “Worsening renal function” the Investigator shall collect an unscheduled laboratory sample for creatinine as soon as judged clinically necessary and initiate follow-up laboratory test of creatinine according to medical judgement. Additionally, the Investigator shall provide information on the medical handling of the AESI, including changes in concomitant treatment.

- Metabolic acidosis, ketoacidosis and diabetic ketoacidosis (DKA)

In case of metabolic acidosis, ketoacidosis and DKA further investigations should be done according to the medical judgement and the clinical course until a diagnosis is made and/or the patient is recovered.

DKA is defined by the diagnostic criteria in the table below, and as defined by the American Diabetes Association (ADA).

Investigators should note that not all criteria in the table below need to apply for the diagnosis of DKA, and clinical judgement should also be taken into consideration. Due to its mechanism of action, empagliflozin may potentially modify the clinical presentation of DKA which may occur at lower plasma glucose levels than stated in the table below.

Table: Diagnostic criteria for DKA

	DKA		
	Mild	Moderate	Severe
Plasma glucose (mg/dL)	>250	>250	>250
Arterial pH	7.25-7.30	7.00-7.24	<7.00
Serum bicarbonate (mEq/L)	15-18	10 to <15	<10
Urine ketones*	Positive	Positive	Positive
Serum ketones*	Positive	Positive	Positive
Effective serum osmolality (mOsm/kg)**	Variable	Variable	Variable
Anion gap***	>10	>12	>12
Alteration in sensoria or mental obtundation	Alert	Alert/drowsy	Stupor/coma

\*Nitroprusside reaction method

\*\*Calculation:  $2[\text{measured Na (mEq/L)} + \text{glucose (mg/dL)}]/18$

\*\*\*Calculation:  $(\text{Na}^+) - (\text{Cl}^- + \text{HCO}_3^-) \text{ (mEq/L)}$

### 9.2.3 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);

- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

#### **9.2.4 Suspected unexpected serious adverse reactions (SUSARs)**

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
  - Summary of Product Characteristics (SPC) for an authorised medicinal product;

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC :

- SUSARs that have arisen in the clinical trial that was assessed by the METC;

- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.

The expedited reporting of SUSARs through the web portal Eudravigilance or ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

### **9.3 Annual safety report**

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

### **9.4 Follow-up of adverse events**

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study, as defined in the protocol.



### **9.5 Data Safety Monitoring Board (DSMB)**

In this trial, an independent DSMB will be established to perform ongoing safety surveillance. The composition, working routines and responsibilities of the DSMB are described in a separate DSMB charter. The independent DSMB will be established before the first subject is included into the study.

The advice(s) of the DSMB will only be sent to the sponsor of the study. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

## **10. STATISTICAL ANALYSIS**

The primary endpoints will be assessed in the intention to treat (ITT) population. This population consists of the population of patients that were actually randomized to one to the two treatment arms and received at least one dose of study medication.

The first assessment will be the calculation of the mentioned response variables in the placebo population including change in dyspnea VAS score at Day 4, diuretic response at Day 4, percentage change in plasma NTproBNP at Day 4 and length of hospital stay. These response variables will be calculated and presented as mean  $\pm$  SD if normal distributed or median (25<sup>th</sup> and 75<sup>th</sup> percentile) in the case non normal distribution is found. For the presentation of baseline characteristics in both treatment arms, continuous variables will be presented as mean  $\pm$  standard deviation, non-normally distributed variables as median (25<sup>th</sup>-75<sup>th</sup> percentile), and categorical variables as count (percentages).

### **10.1 Primary study parameter(s)**

The primary analysis of the treatment effect of the randomized treatment will be carried out in the ITT population. For each individual response variable for the primary continuous outcome measure we estimate a treatment effect of 0.48 standard deviations, at the two sided 20% significance level (P value 0.2), with 80% power. The difference in the continuous response variables between the two treatment groups will be analysed using a t-test, assuming normality of these continuous variables. Since this primary outcome measure consists of an exploratory analysis, a conservative P value of 0.2 for significance will be used, and no correction for multiplicity will be adopted.

As exploratory analysis, individual responses (for the continuous response variables) will be standardized, and log rank scores for time to event outcomes will be standardized. Using this approach the standardized mean difference between treatment groups will be calculated. Furthermore, these standardized responses will be averaged across the primary outcome response variables, resulting in a mean standardized response score, from which a mean standardized response score difference may be estimated between treatments and assessed using t-test.

### **10.2 Secondary study parameter(s)**

Secondary response variable include death and/or heart failure re-admission through Day 30 which will be assessed using logistic regression analysis for the between treatment difference. Changes in biomarkers and the difference in change between treatment groups, including plasma or urinary biomarkers will be assessed using t-test for normal distributed variables and Wilcoxon rank sum test if non-normally distributed.

### **10.3 Other study parameters**

Adverse event rates between treatment groups will be analysed using Fisher's exact tests, and presented as counts (percentages).

## **11. ETHICAL CONSIDERATIONS**

### **11.1 Regulation statement**

The study will be conducted according to the principles of the Declaration of Helsinki (64<sup>th</sup> WMA General Assembly, October 2013), and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts (GCP, GMP).

### **11.2 Recruitment and consent**

Recruitment of patients will take place through continuous monitoring of the Emergency Room admissions. Once a potentially eligible patient is admitted to the Emergency Room, and the diagnosis acute heart failure has been established, the Principal Investigator or a sub-investigator (physician) will verify eligibility based on hospital charts. Once eligibility has been established, the supervising cardiologist will be asked for permission to ask the patient for consent to participation in the study. After approval by the supervising cardiologist, the Principal Investigator or sub-Investigator will approach the patient, and

ask whether he/she is potentially interested in participation in the study. Interested patients will be provided with the patient information leaflet and they will be given verbal information about the study. Patients will be adequate time to consider their decision and to ask questions. Once a patient remains interested in participation, the Principal Investigator or sub-Investigator will go through all study details once again and then the patient signs and dates the informed consent form first, after which the Principal Investigator or sub-Investigator will sign and date the informed consent form, too. Before having obtained written informed consent from the patient, no study related assessments will be performed.

### **11.3 Objection by minors or incapacitated subjects (if applicable)**

Not Applicable

### **11.4 Benefits and risks assessment, group relatedness**

Empagliflozin has been shown to be relatively safe and well tolerated by patients with Diabetes Mellitus Type 2, and in heart failure patients with NYHA II-III heart failure it proved to reduce overall mortality. Based on these finding, the relative risk is estimated to be relatively low, while potential benefit may be expected.

### **11.5 Compensation for injury**

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

## **12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION**

### **12.1 Handling and storage of data and documents**

A subject identification code list will be made to link the data to the subject in order to be able to trace data to an individual subject. This code will not be based on the patient initials and birth-date. The key to the code will be safeguarded by the investigator since the data will be kept for a period of 15 years. The handling of personal data will comply

with privacy laws, legislation, codes and/or guidelines that apply in the applicable jurisdictions the study is conducted.

## **12.2 Monitoring and Quality Assurance**

Independent monitors will monitor the study in each country according to a pre-specified monitoring plan. The monitors are trained in GCP and will be trained on study specific tasks and processes. As part of the UMCG Quality Management Strategy monitor oversight will be implemented through regular documentation reviews and co-monitoring activities.

## **12.3 Amendments**

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

## **12.4 Annual progress report**

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

## **12.5 Temporary halt and (prematurely) end of study report**

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

## **12.6 Public disclosure and publication policy**

The trial will be registered in a public trial registry. The results will be disclosed unreservedly.

## **13. STRUCTURED RISK ANALYSIS**

### a. Level of knowledge about mechanism of action

Empagliflozin is a reversible, highly potent (IC<sub>50</sub> of 1.3 nmol) and selective competitive inhibitor of sodium-glucose co-transporter 2 (SGLT2). Empagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is 5000 times more selective for SGLT2 versus SGLT1, the major transporter responsible for glucose absorption in the gut. SGLT2 is highly expressed in the kidney, whereas expression in other tissues is absent or very low. It is responsible, as the predominant transporter, for the reabsorption of glucose from the glomerular filtrate back into the circulation. In patients with type 2 diabetes and hyperglycaemia a higher amount of glucose is filtered and reabsorbed.

Empagliflozin improves glycaemic control in patients with type 2 diabetes by reducing renal glucose reabsorption. The amount of glucose removed by the kidney through this glucuretic mechanism is dependent on blood glucose concentration and GFR. Inhibition of SGLT2 in patients with type 2 diabetes and hyperglycaemia leads to excess glucose excretion in the urine.

In patients with type 2 diabetes, urinary glucose excretion increased immediately following the first dose of empagliflozin and is continuous over the 24 hour dosing interval.

Increased urinary glucose excretion was maintained at the end of the 4-week treatment period, averaging approximately 78 g/day. Increased urinary glucose excretion resulted in an immediate reduction in plasma glucose levels in patients with type 2 diabetes.

Empagliflozin improves both fasting and post-prandial plasma glucose levels. The mechanism of action of empagliflozin is independent of beta cell function and insulin

pathway and this contributes to a low risk of hypoglycaemia. Improvement of surrogate markers of beta cell function including Homeostasis Model Assessment- $\beta$  (HOMA- $\beta$ ) was noted. In addition, urinary glucose excretion triggers calorie loss, associated with body fat loss and body weight reduction. The glucosuria observed with empagliflozin is accompanied by mild diuresis which may contribute to sustained and moderate reduction of blood pressure.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

All of the drugs used in the study have been used extensively in clinical trials of patients with type 1 and type 2 diabetes and have been granted marketing approval for the treatment of cardiovascular complications in type 2 diabetes. Empagliflozin is currently being tested in patients with congestive heart failure. The present study is the first study in patients with acute heart failure with or without diabetes.

c. Can the primary or secondary mechanism be induced in animals and/or in ex-vivo human cell material?

Empagliflozin has been studied extensively in animals and human cell material before performing clinical trials in humans and generally the primary and secondary mechanisms can be induced in animals.

d. Selectivity of the mechanism to target tissue in animals and/or human beings

Empagliflozin selectively binds to the SGLT2 receptor, and is > 5000 times more selective for SGLT2 versus SGLT1, which is the major transporter in the gut responsible for glucose absorption.

e. Analysis of potential effect

The empagliflozin dose used in this trial has been safely used in trials of patients with type 2 diabetes, renal impairment, and heart failure.

f. Pharmacokinetic considerations

In vitro data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by uridine 5'-diphosphoglucuronosyltransferases UGT1A3, UGT1A8, UGT1A9, and UGT2B7. Empagliflozin is a substrate of the human uptake transporters OAT3, OATP1B1, and OATP1B3, but not OAT1 and OCT2. Empagliflozin is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

Co-administration of empagliflozin with probenecid, an inhibitor of UGT enzymes and OAT3, resulted in a 26% increase in peak empagliflozin plasma concentrations ( $C_{max}$ ) and a 53% increase in area under the concentration-time curve (AUC). These changes

were not considered to be clinically meaningful. The effect of UGT induction on empagliflozin has not been studied. Co-medication with known inducers of UGT enzymes should be avoided due to a potential risk of decreased efficacy. An interaction study with gemfibrozil, an in vitro inhibitor of OAT3 and OATP1B1/1B3 transporters, showed that empagliflozin C<sub>max</sub> increased by 15% and AUC increased by 59% following co-administration. These changes were not considered to be clinically meaningful. Inhibition of OATP1B1/1B3 transporters by co-administration with rifampicin resulted in a 75% increase in C<sub>max</sub> and a 35% increase in AUC of empagliflozin. These changes were not considered to be clinically meaningful. Empagliflozin exposure was similar with and without co-administration with verapamil, a P-gp inhibitor, indicating that inhibition of P-gp does not have any clinically relevant effect on empagliflozin. Interaction studies conducted in healthy volunteers suggest that the pharmacokinetics of empagliflozin were not influenced by co-administration with metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, simvastatin, torasemide and hydrochlorothiazide.

Based on in vitro studies, empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. Empagliflozin does not inhibit UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. Drug-drug interactions involving the major CYP450 and UGT isoforms with empagliflozin and concomitantly administered substrates of these enzymes are therefore considered unlikely. Empagliflozin does not inhibit P-gp at therapeutic doses. Based on in vitro studies, empagliflozin is considered unlikely to cause interactions with drugs that are P-gp substrates. Empagliflozin does not inhibit human uptake transporters such as OAT3, OATP1B1, and OATP1B3 in vitro at clinically relevant plasma concentrations and, as such, drug-drug interactions with substrates of these uptake transporters are considered unlikely. Interaction studies conducted in healthy volunteers suggest that empagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, simvastatin, warfarin, ramipril, digoxin, diuretics and oral contraceptives.

#### g. Study population

Patients with acute heart failure are included in this study. The patients are admitted to emergency department and/or at the cardiac care unit and are under close monitoring of treating physicians.

#### h. Interaction with other products

See “f” for PK interaction with other products.

#### i. Predictability of effect

Previous studies with empagliflozin have suggested that the drug decreases extracellular volume and exerts a natriuretic diuretic effects. On the basis of these findings we anticipate that empagliflozin may be beneficial for patients with acute heart failure.

j. Can effects be managed?

Patients are regularly monitored and asked about adverse effects.

### **13.1 Synthesis**

In this study adverse events of special interest are collected. These include hepatic injury, decreased renal function and metabolic acidosis. These side effects are rare but will be monitored closely by regular monitoring of liver enzymes, serum creatinine, and metabolic acidosis. The potential benefits of empagliflozin to decrease complications of acute heart failure clearly outweigh the risk of developing these adverse events.

## **14. REFERENCES**

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